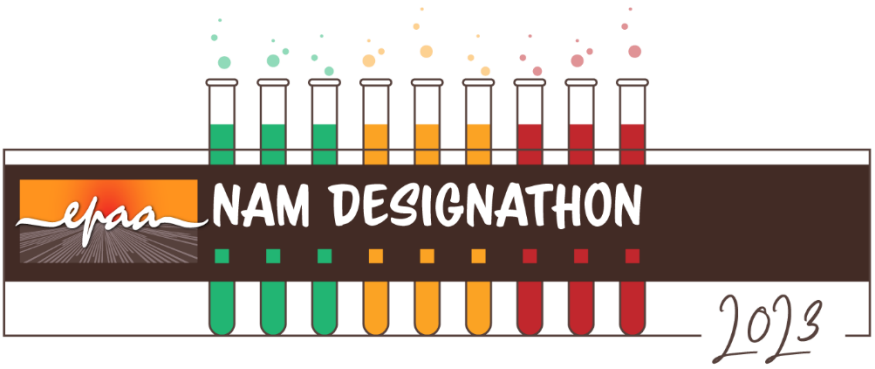
**NAM DESIGNATHON 2023**

**The EPAA Designathon for human systemic toxicity**




There is a pressing need to better assess and manage the risks of chemicals. Robust information is available for only a very small proportion of the estimated 100,000 chemicals on the market, with many substances having limited information[1].

In collaboration with the EPAA, the JRC has developed a vision for "Chemicals 2.0", a cross-sector approach to safety assessment and risk management with three main objectives:

1) Evaluate all chemicals on the market according to their concern level, through an improved understanding of their hazard and exposure
2) Introduce NAMs[2] during a phase-in period and establish confidence in their regulatory use
3) Replace eventually all animal testing associated with assessment and management of the risks of chemicals

To achieve this vision, one goal is the need to develop an alternative approach to hazard classification, based solely on the use of NAMs for systemic toxicity. A new classification scheme should be designed to ensure equivalent protection, by capturing substances already classified, but will also increase the overall protection level, by assessing substances not currently classified due to lack of information.

**"Levels of concern" as the basis of equivalent protection**

The aim is to explore the design of a future classification system identifying three levels of concern (high, medium and low) based on the use of NAMs that provide information on the toxicodynamic and toxicokinetic properties of chemicals, referred to here as activity and potential systemic availability (see Figure and FAQs for definitions).

[1]EEA State of the Environment (2019), p239. https://www.eea.europa.eu/soer/publications/soer-2020

[2]This EPAA Project uses the definition of NAMs proposed by ECHA (2016) and built on by US EPA (2018) " ... a broadly descriptive reference to any technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment that avoids the use of intact animals".

| | | Activity (NAM-based toxicodynamics) | | |
|---|---|---|---|---|
| | | **High** | **Medium** | **Low** |
| **Potential Systemic Availability** (NAM-based toxicokinetics, based on ADME properties) | **High** | H | H | M |
| | **Medium** | H | M | L |
| | **Low** | M | L | L |

In a future EU classification system for systemic toxicity, it is proposed that **low concern chemicals (L)** could be used without restriction (supporting safety by design), **medium concern chemicals (M)** would require risk assessment to establish safe use levels, while **high concern chemicals (H)** would be candidates for risk management.

**Challenge to the NAM development community**

The EPAA invites the submission of NAM-based solutions to inform the development of a future classification system for systemic toxicity of human health based on the activity and potential systemic availability of chemicals.

- The NAM-based classifications should reflect levels of concern related to, but not synonymous with, the current classification system addressing systemic toxicity.
- The NAMs do not need to literally predict the outcomes of animal studies. Nor are they expected to reproduce existing classifications.

The EPAA will provide a **reference list** of approx. 150 chemicals, along with identifiers (name, CAS No, SMILES), reflecting the three levels of concern. The number of chemicals in each class (High, Medium and Low) will also be provided. However, no further information will be provided (i.e. which chemical belongs to which class).

The challenge is to propose prototype NAM-based solutions that categorise some or all of the chemicals on the reference list. In this initial prototype phase, specific data generation is not necessarily required, but rather ideas for a NAM-based classification scheme can be explored using existing information. The EPAA will provide a **reporting template**, including guidance.

**There will be no winning solution**

Instead, in this pilot phase, the aim will be to compare and contrast the different solutions suggested by all of the participants in terms of their outputs (classifications or not being able to derive a classification), types of data used (input parameters), methods (in vitro, in silico, in chemico), data interpretation procedure and underpinning scientific rationale. All participants will be invited to this discussion and it is foreseen that this analysis will be informative in itself and pave the way for further EPAA activities. In particular, it is foreseen that the second phase the EPAA designathon will focus on the co-creation of hybrid solutions.

**Timeline**

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|---|---|
| 31 May – 01 June 2023 | Presentation at the ECHA workshop: 'New approach methodologies workshop: Towards an animal free regulatory system for industrial chemicals' |
| 01 June 2023 | Web announcement by EPAA |
| Early July 2023 | Orientation webinar(s) for all |
| 1 August 2023 | Deadline to register interest for pilot phase |
| As soon as participants register interest | Formal start of the EPAA designathon pilot phase. Participants receive reference list of chemicals and reporting template/guidance. |
| 31 December 2023 | Deadline to submit pilot phase solutions |
| January 2024 | EPAA team to structure the workshop based on submitted solutions |
| End February/early March 2024 | Workshop to discuss pilot phase solutions with submitters |

## Frequently asked questions

**1) Will participants be given the assigned classifications for the reference chemicals?**

No, participants will only be given the list of chemical identifiers (including names, CAS Nos and SMILES) and the prevalence of chemicals in each category (H, M and L). This is to avoid the development of over-fitted solutions and to encourage reliance on scientific reasoning.

**2) What is the rationale for the assigned classifications?**

The EPAA team will assign each reference chemical to one of the H, M and L categories using publicly available information on the systemic toxicity profile of the chemical. The assigned classifications take into account existing harmonised classifications for systemic toxicity.

**3) Are there any constraints on which NAMs can be used?**

No, all kinds and combinations of NAMs can be used. Practicalities such as cost and deployability are not considered at this stage, since the aim is to identify useful types of toxicokinetic and toxicodynamic information, along with the rationale for their use.

**4) Can existing data be used?**

Yes, provided the data are derived from NAMs. In vivo (animal or human) data on the chemicals from the reference list are excluded. There are numerous public resources providing access to NAM data.[3] Ideally, your NAM based approach to (repeated dose) systemic toxicity should be built to inform on the classification of chemicals for humans, but we are aware that the majority of today's knowledge on (repeated dose) systemic toxicity is based on effects in animals. Hence, if your NAM is calibrate based on historic animal data, this should be indicated.

**5) Can read-across be proposed?**

Yes, provided that the read-across is based on a defined approach (prediction model). In other words, subjective read-across based on expert judgement is excluded, since this is not reproducible. Suitable read-across algorithms can be based on chemical and/or biological similarity.

**6) Can participants propose an alternative classification matrix?**

The classification matrix is intended to convey the general concept – that equivalent protection can be based on the classification of chemicals into three categories, according to the level of concern for systemic effects, based on both "activity" and "potential systemic availability". In addition to a three-level classifier, it is permissible for a NAM-based solution to distinguish between Low Concern chemicals and the rest (M and H), or between High Concern chemicals and the rest (M and L).

**7) In the classification matrix, what is meant by Activity?**

A NAM-based toxicodynamic attribute. The extent to which a chemical is expected to perturb the biology of human cells, tissues and organs, according to the nature and potency of its effect(s) measured in vitro and/or computed in silico. The activity profiles of different chemicals should be indicative of/related to adversity and can be compared without the need for information on external human exposure levels associated with particular uses of the chemical.

[3]Madden et al (2020). A Review of In Silico Tools as Alternatives to Animal Testing: Principles, Resources and Applications. ATLA 48(4):146-172. doi:10.1177/0261192920965977

8) **In the classification matrix, what is meant by Potential Systemic Availability?**

A NAM-based toxicokinetic attribute. The extent to which a chemical is expected to reach the systemic circulation and cells/tissues/organs, according to its ADME / toxicokinetic properties measured in vitro and/or computed in silico. The Potential Systemic Availabilities of different chemicals and relevant metabolites can be compared without the need for information on external human exposure levels associated with particular uses of the chemical.

9) **Must all reference chemicals be addressed?**

No, solutions may focus on a subset of the reference chemicals. More important is the reasoning underlying the proposed NAMs and the resulting classifications. An attempt should be made to define the applicability domains of the NAMs used.

10) **Should the NAM-based classifications be accompanied by an expression of uncertainty?**

Ideally, yes. Classifiers with probabilistic results are encouraged. As in other cases, the underlying methodology should be described.

11) **Can additional reference chemicals and their classifications be proposed?**

Yes, provided that this information contributes to the rationale for the NAM-based solution and classifications for the EPAA-selected reference chemicals. This information may be used in a further phase.

12) **Do I need to disclose NAM data?**

At this stage, we are not requesting the raw data generated by NAMs (e.g. in vitro readouts). Instead, we are interested in how the data are used to make predictions/classifications, and in the underlying scientific rationale. At a later stage, there may be an interest to integrate multiple datasets for further analysis, but this will require the agreement of the data owners.

13) **Will any NAM data I provide be used to make regulatory decisions?**

This is a research exercise, not a regulatory procedure. In case NAM data are provided, these will be used to inform the evolution of NAM-based solutions, and only made public with the agreement of the data owner.

14) **What if my NAM contains proprietary elements?**

Any elements that are covered by intellectual property should be identified during the submission.

15) **Will the information shared during the workshop be made public?**

The content of any workshop proceedings will be agreed by the participants. Most likely, a workshop report will summarise the high-level findings and recommendations, rather than details of specific NAMs.